Tretinoin Overdose: A First Case Report

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ABSTRACT

Introduction: Tretinoin (Vesanoid) is an all-*trans*-retinoic acid, and is related to retinol (Vitamin A). To date, there have been several case reports on overdose with its isomer isotretinoin, but none involving overdose of tretinoin. We report the first known case of a patient who ingested a massive overdose of tretinoin.

Case Report: A 31-year-old man ingested 1000 mg of tretinoin (100 pills of Vesanoid 10 mg) in a suicide attempt. He developed nonbloody diarrhea, but otherwise had no complaints. Clinical examination was normal. The patient was treated with activated charcoal and was hydrated. The patient's blood results did not show any deterioration on the third consecutive day. He was discharged well on the third day, but was subsequently lost to follow-up.

Discussion: Although there has been no reported experience with acute tretinoin overdose in humans, our patient took a dose approximately 3 times the recommended maximum tolerated daily dose in patients with myelodysplastic syndrome or solid tumors (195 mg/m^2 per day). Overdose with other retinoids such as isotretinoin have been associated with only minor symptoms that resolved quickly. Our patient had diarrhea, which also resolved quickly with symptomatic treatment and hydration.

Conclusion: We believe this to be the first case report of an acute oral overdose of tretinoin. The patient developed diarrhea, but was otherwise asymptomatic.

INTRODUCTION

Tretinoin (Vesanoid) is an all-*trans*-retinoic acid, and is related to retinol (Vitamin A) [1]. As Vitamin A derivatives, retinoids are important regulators of cell reproduction, proliferation, and differentiation [2]. Tretinoin is indicated for the induction of complete remission in patients with acute promyelocytic leukemia [3–5]. The Food and Drug Administration (FDA) originally approved tretinoin as a topical agent for acne in 1971, and tretinoin capsules were approved in November 1995. Although both are retinoids, tretinoin and Vitamin A have differences in their mechanism of transport and metabolism [6].

To date, there have been several case reports of overdose of its synthetic 13-*cis* isomer isotretinoin [7–11], but no reports of tretinoin overdose. We report the first case of a patient who ingested approximately 1000 mg of tretinoin.

CASE REPORT

A 31-year-old man with a history of acquired immunodeficiency syndrome (AIDS), acute promyelocytic leukemia in remission,

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gout, and chronic renal insufficiency due to a congenital single kidney was taking multiple daily medications including Vesanoid, lamivudin (Epivir), Viogen (Vitamin B complex with C and minerals), fenofibrate (TriCor), lisinopril, allopurinol, acyclovir and testosterone (AndroGel). In a suicide attempt, he ingested 100 pills of Vesanoid (10 mg each). Soon after the ingestion, he decided to inform his partner and was immediately brought to an emergency department (ED), arriving within an hour of the ingestion. He was given an oral dose of activated charcoal and infused with normal saline in dextrose 5%, intravenously.

The patient developed nonbloody diarrhea in the ED, but otherwise had no complaints. His vital signs were normal, and his clinical examination was unremarkable. Toxicology studies, including serum assays for aspirin and acetaminophen and a urine screen for drugs of abuse, were negative. He was noted to have a baseline creatinine level of 3–3.5 mg/dL (260–300 mmol/L) due to his underlying renal insufficiency from a congenital single kidney. Because of concerns about the potential for toxicities such as retinoic acid acute promyelocytic leukemia syndrome (RA-APL, characterized by fever, acute respiratory distress, and multi-organ failure), thrombosis, and pseudotumor cerebri, which have been associated with the therapeutic use of tretinoin [1,12,13], and fearing the possibility of further renal deterioration, the patient was admitted for observation and monitoring.

On admission, white blood cells were 5300/μL; platelets were 130,000/μL, hemoglobin was 12.2 g/dL, hematocrit was 33.4%, blood urea nitrogen was 38 mg/dL (13.6 mmol/L), and creatinine was 3.5 mg/dL (308 mmol/L). The next day, his hemoglobin fell to 10.2 g/dL, and hematocrit was 28.5%. There was no reported evidence of gastrointestinal blood loss or hemolysis. However, his hemoglobin level remained stable (10.3 g/dL) when repeated on the third day after admission. The patient was managed symptomatically. He did not have complaints after his diarrhea rapidly resolved. The patient's blood results did not show any deterioration on the third consecutive day.

After psychiatric assessment, the patient was discharged on the third day. He was instructed to continue his medications in the same way as he did prior to the overdose. He was discharged to his primary care physician, but was subsequently lost to follow-up.

DISCUSSION

We believe that this is the first reported case of a patient with a large intentional overdose of tretinoin.

Tretinoin activity is primarily due to the parent drug. It is a first-generation retinoid that induces maturation of acute promyelocytic leukemia cells in culture [14]. It induces leukemic cell differentiation and complete remission in a high proportion of patients with acute promyelocytic leukemia (APL) [15]. It targets the specific molecular lesion in APL and has theoretical appeal because it avoids the nonspecific toxicity [13,15] of conventional chemotherapeutic drugs. It is often used for those who are refractory to conventional drugs, have relapsed, or in whom anthracycline chemotherapy is contraindicated [1]. The exact mode of action of tretinoin in APL is unknown. Treatment produces an initial maturation of the primitive promyelocytes derived from the leukemic clone, followed by a repopulation of the bone marrow and peripheral blood by normal, polyclonal hematopoietic cells in patients achieving complete remission [1].

Although our patient presented soon after his overdose, we believe that a significant amount of drug was already absorbed into the systemic circulation, given the rapid time to peak concentration of 1–2 hours [1]. Tretinoin has an elimination half-life of 0.5 to 2 hours in patients with APL and is >95% bound in plasma, mainly by albumin. Its metabolites include 13-*cis*-retinoic acid, 4-oxo-*trans*-retinoic acid and 4-oxo-*trans*-retinoic acid glucuronide. It is excreted mainly in the urine and feces [1].

Tretinoin is supplied as 10-mg capsules [1]. The recommended dose by the manufacturer is 45 mg/m^2 per day until complete remission. Therapy is discontinued 30 days after achieving complete remission or after 90 days of treatment, whichever comes first [1]. Although there has been no experience with acute overdose in humans, the maximum tolerated dose in patients with myelodysplastic syndrome or solid tumors was 195 mg/m^2 per day [1]. Our patient was a slender male, which makes his overdose about 3 times higher than the maximum tolerated dose ever reported. Overdose with other retinoids such as isotretinoin are reported to cause transient headache, facial flushing, cheilosis, abdominal pain, dizziness, and ataxia, but the symptoms quickly resolve without apparent residual effects [7–11]. Our patient had diarrhea that also resolved quickly with symptomatic treatment. He also had an unexplained drop in his hemoglobin level from 12.2 g/dL to 10.2 g/dL. There was no reported evidence of gastrointestinal blood loss, nor were tests done to rule out hemolysis in this patient. However, the hemoglobin level remained stable (10.3 g/dL) when repeated on the third day after admission, and the initial drop was thought to be secondary to dilution from the fluids that the patient received.

Treatment for overdose is supportive as there is no specific antidote. The manufacturer recommends that the patient with overdose should be treated in a special hematological unit [1] because of the risk of retinoid toxicity or possible fatal thrombotic complications, although there have been no documented cases to date.

Adverse effects associated with therapeutic doses of tretinoin include headache, pseudotumor cerebri, dry skin, cheilosis, scrotal excoriations [16], musculoskeletal aches, bone pain, bone marrow necrosis [17], hypertriglyceridemia, respiratory distress, and transient hepatic dysfunction to severe liver toxicity [13,18]. Retinoic acid syndrome (RA-APL) is potentially fatal, characterized by fever, respiratory distress, interstitial pulmonary infiltrates, pleural effusions, and weight gain [19]. This occurs in up to 25% of patients with APL treated with Vesanoid [1]. Treatment of this complication involves early administration of high-dose steroids [13].

Unfortunately, a tretinoin drug level was not obtained in this patient, although it should be assumed that this was a legitimate ingestion, given the clinical scenario.

CONCLUSION

In our patient with tretinoin overdose, the only observed effect was mild diarrhea.

The authors have no potential financial conflicts of interest to report.

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